RESEARCH

COMPARISON OF CLINICAL OUTCOMES OF CORONAVAC VACCINATED AND UNVACCINATED OLDER ADULTS WITH HOSPITALIZED COVID-19

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Abstract

Introduction: We aimed to compare the COVID-19 outcomes in unvaccinated and CoronaVac vaccinated older adults.

Materials and Method: In this single-center study, patients aged ≥65 years who were hospitalized for COVID-19 were retrospectively analyzed in two groups: unvaccinated and vaccinated.

Results: A total of 742 patients were included. The mean age was 76.6±7.6 years. Of these, 46.1% (n=342) were male, 76.0% (n=564) were vaccinated. Among patients who were transferred to the intensive care unit (n=217), 206 (27.8%) received invasive mechanical ventilation support and 194 (26.1%) were died. In the multivariate analysis, advanced age (OR=1.03, 95%CI=1.01-1.06, p<0.01) and a high Charlson Comorbidity Index (OR=1.24, 95%CI=1.12-1.38, p<0.01) were predictors of mortality, while being vaccinated (OR=0.75, 95%CI=0.62-0.91, p<0.01) was associated with survival. Vaccination reduced the need for intensive care by 26.5% and mortality by 24.9 %. When the vaccinated group was evaluated, high Charlson Comorbidity Index (OR=1.428, 95%CI=1.14-1.64, p<0.01) was an independent predictor for mortality. However, booster vaccination in the last 130 days was the only protective factor that reduced mortality (p=0.04, 95%CI=0.43-0.99, OR=0.66) in multivariate analysis. Booster dose vaccination in the last 130 days reduced mortality by 33.8%.

Conclusion: CoronaVac vaccination improved survival in hospitalized older adult patients (≥65 years old) with COVID-19. However, delaying the booster dose for more than 130 days were significantly associated with decreased survival. Therefore, older adults who completed their primary vaccination series with CoronaVac should not delay their booster dose to reduce the risk of death.

Keywords: COVID-19; Aged; Death; Vaccination.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was unexpectedly resulted in a global pandemic with significant disruption and many loss of life. In response, an extraordinary effort has been made to develop vaccines against SARS-CoV-2 (1). Mass vaccination programs with newly approved COVID-19 vaccines have been implemented all around the world, giving priority to high-risk individuals to induce protective immunity and control the spread of SARS-CoV-2 (2).

CoronaVac (Sinovac Biotech), an inactivated whole virus vaccine, is the first vaccine approved in Turkey. The vaccination campaign for CoronaVac started on January 14, 2021. For this reason, most healthcare workers and older adults in the high-risk group in our country were vaccinated with CoronaVac (3). The World Health Organization's Emergency Use Listing (WHO EUL) procedure approved the use of the CoronaVac vaccine in early June 2021, but stated that new evidence-based information is needed on its efficacy and safety in adults aged ≥ 60 years (4). However, in an observational study in Chile, referred by WHO EUL, adjusted vaccine efficacy in people aged ≥ 60 years was 66.6% for the prevention of COVID-19, 85.3% for the prevention of hospitalization, 89.2% for the prevention of admission to the intensive care unit, and 86.5% for prevention of COVID-19 related death (5).

Our 1000-bed hospital was built as a pandemic epicenter where only COVID-19 patients were hospitalized in Istanbul, which is the most populated city of Turkey. In this study, we aimed to compare CoronaVac vaccinated and unvaccinated patients aged ≥ 65 years who were hospitalized with COVID-19 in the delta (B.1.617.2) variant dominant period in terms of disease severity, need for admission to the intensive care unit (ICU), and death. In addition, we determined the factors affecting the severity of COVID-19 in vaccinated patients and evaluated the effect of booster vaccine doses on survival.

MATERIALS AND METHOD

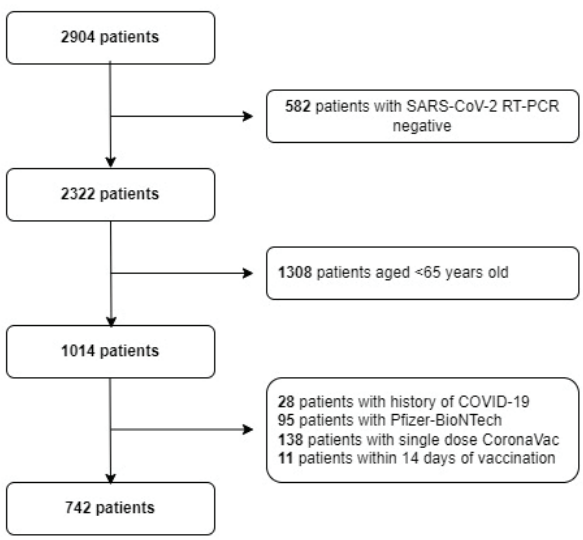
Study Design

This was an analytical, cross-sectional, epidemiological study. Patients aged ≥ 65 years who were hospitalized for COVID-19 in a tertiary care hospital between September 1, 2021 and December 15, 2021, were included. Patients who had at least two doses of CoronaVac vaccine were defined as "vaccinated", and patients who did not receive any vaccine were defined as "unvaccinated".

Inclusion criteria were as follows: (1) patients aged ≥ 65 years; (2) positive testing for SARS-CoV-2 by real-time polymerase chain reaction (RT-PCR); and (3) hospitalization for COVID-19. Exclusion criteria were as follows: (1) previous history of confirmed COVID-19; (2) patients vaccinated with a single dose of CoronaVac; (3) patients who received Pfizer-BioNTech as the primary vaccination; and (4) patients who had COVID-19 14 days after the 2nd dose.

A total of 2162 of the 2904 patients were excluded (Figure 1). Demographic characteristics includ-

Figure 1. Flow diagram demonstrating patient enrollment



ing age, sex, underlying diseases, clinical features, laboratory findings, vaccination status, admission to the intensive care unit, need for mechanical ventilation, and clinical outcomes were retrospectively collected from medical charts and electronic medical records.

The primary outcomes were the need for ICU admission and death in hospitalized patients with COVID-19. The secondary outcome was death in vaccinated patients with COVID-19.

The following criteria were used according to WHO definitions to determine disease severity (6).

• Critical COVID-19: Sepsis, septic shock, acute respiratory distress syndrome (ARDS), or conditions that cause necessary treatments for survival, such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy

• Severe COVID-19: SpO2 <90% on room air; or respiratory rate>30 breaths/min; or signs of severe respiratory distress

• Non-severe COVID-19: Absence of any criteria for severe or critical COVID-19.

According to the Republic of Turkey Ministry of Health COVID-19 Guideline, favipravir (2 x 1600 mg loading on the first day, 2 x 600 mg in the next four days) was started in all patients with COVID-19 and decord 6 mg or prednol 40 mg was started in those with a room air oxygen saturation <92% (7).

The Charlson Comorbidity Index (CCI) was used to evaluate the comorbidity status of the patients. Mortality was defined as the in-hospital death.

Statistical analysis

Continuous variables were expressed as mean and standard deviation, while categorical variables were expressed as percentages (%) and frequencies (n). The normal distribution of the data questioning the necessity of using the parametric test was evaluated using Kolmogorov-Smirnov test, Kurtosis and Skewness tests. According to the normality of the distribution, appropriate parametric or non-parametric tests were applied.

Univariate logistic regression analysis was performed to identify the factors causing death in COVID-19 and to detect poor prognostic predictors in vaccinated patients. All factors with $p<0.05$ were included in the multivariate logistic regression analysis. Kaplan Meier analysis was applied to compare the expected survival status in vaccinated and unvaccinated patients with COVID-19.

The results were evaluated using a 95% confidence interval (CI) with a p-value < 0.05. IBM SPSS-21 (Statistical Package for Social Sciences, Armonk, NY, USA) was used for statistical analyses.

Ethical Approval

This study was approved by local ethics committee (Decision No: 2022-14-10, Date: 18.07.2022). Written informed consent was waived, given the retrospective nature of this study.

RESULTS

In total, 742 patients were included in the study. There were 342 male patients (46.1%), and the mean age was 76.6 ± 7.6 years. Regarding the immunization status, 564 (76.0%) patients were vaccinated and 178 (24.0%) were unvaccinated. Among those vaccianted, 281 patients received a third booster dose. Of these patients, 71.5% (n = 201) received the CoronaVac and 28.5% (n = 80) received the Pfizer-BioNTech vaccine. The mean ages of vaccinated and unvaccinated patients were similar (76.8 ± 7.5 years versus 76.2 ± 7.9 years, p = 0.32). The mean length of hospital stay was 13.9 ± 10.8 days. Ferritin (551 ± 749 µg/L versus 714 ± 817 µg/L, p < 0.01), alanine aminotransferase (ALT) (24 ± 24 IU/L versus 30 ± 27 IU/L, p < 0.01), and aspartate transaminase (AST) levels (35 ± 39 IU/L versus. 42 ± 41 IU/L, p < 0.01) were lower in vaccinated patients than in unvaccinated patients. Leukocyte count (p = 0.95), procalcitonin (p = 0.89), C-reactive protein (CRP) (p

= 0.09), creatinine (p = 0.06), and D-dimer levels (p = 0.12) did not significantly differ between groups. A comparison of demographic features, clinical characteristics, and biochemical parameters of the patients with vaccinated and unvaccinated is shown in Table 1.

The mean CCI in the vaccinated group was higher than in the unvaccinated group (5.6±1.6 vs. 5.1±1.8, p<0.01). Comorbidities, of at least one present, were more frequent in vaccinated patients (n = 487, 86.3%) than in unvaccinated patients (n = 138, 77.5%) (p < 0.01). The most frequent comorbidities were hypertension (n = 491, 66.1%), diabetes mellitus (n = 284, 38.2%), coronary artery disease (n = 173, 23.3%), and asthma/*chronic obstructive pulmonary disease (COPD)* (n = 94, 12.7%). Hypertension (68.3% versus 59.5%, p = 0.03), diabetes mellitus (41.5% versus 28.1%, p < 0.01), and coronary artery disease (26.7% versus. 12.4%, p < 0.01) were higher in vaccinated patients than in unvaccinated patients (Table 1). In the subgroup analysis, there was no significant difference in mortality between the vaccinated and unvaccinated patients according to comorbidities (Table 2). There was no comorbidity in 13.7% (n = 77/564) of the vaccinated patients and 22.5% (n = 40/178) of the unvaccinated patients (p < 0.01). In the subgroup analysis, the need for ICU admission was 22.1% in the vaccinated patients (n = 17/77) and 42.5% in the unvaccinated patients (n = 17/40) (p=0.02). In hospital death was higher in the unvaccinated patients (n= 14, 35.0%) compared to vaccinated patients (n = 13, 16.8%) (p = 0.03).

Of the 742 patients with COVID-19, 29.8% had mild disease (n = 221), 38.3% had severe disease (n = 284), and 31.9% had critical disease (n = 237). While non-severe and severe diseases were more common in vaccinated patients, critical diseases were more common in unvaccinated patients (p = 0.03). Among the total, 217 (29.2%) patients were followed up in the ICU, 206 (27.8%) patients required invasive mechanical ventilation, and 194 (26.1%) patients died. The need for ICU admission (n = 66, 37.1%, versus n = 151, 26.8%, p = 0.01), invasive mechanical ventilation support (n = 63, 35.4%, versus n = 143, 25.4%, p = 0.01), and mortality (n = 58, 32.6%, versus n= 136, 24.1%, p = 0.03) were higher in the unvaccinated group than in the vaccinated group.

In the multivariate analysis, advanced age (OR = 1.03, 95% CI = 1.00–1.05, p = 0.01) and high CCI (OR = 1.21, 95% CI = 1.09–1.34, p < 0.01) were associated with increased need for ICU admission while being vaccinated (OR = 0.73, 95% CI = 0.61–0.89, p < 0.01) was found to be the protective factor. Similarly, advanced age (OR = 1.03, 95% CI = 1.01–1.06, p < 0.01) and high CCI (OR = 1.24, 95% CI = 1.12–1.38, p < 0.01) were predictors of mortality. However, being vaccinated (OR = 0.75, 95% CI = 0.62–0.91, p < 0.01) was associated with survival in the multivariate analysis. Vaccination reduced the need for ICU admission by 26.5% (95% CI = 11–39) and mortality by 24.9 % (95% CI = 9–38).

Among the vaccinated patients, death was more common in patients with advanced age (p = 0.01), high CCI (p < 0.01) and chronic kidney disease (p = 0.03). Mortality was lower in patients who received a booster dose during the last 130 days (20.0% versus 27.4%, p = 0.04) (Table 3). There was no significant difference between patients who had booster dose of CoronaVac and Pfizer-BioNTech in terms of the need for ICU admission (21.4% versus 28.7%, p = 0.19) or death (18.4% versus 26.2%, p = 0.14). We found that high CCI was an independent predictor of ICU admission (OR = 1.25, 95% CI = 1.11–1.41, p < 0.01) and death (OR = 1.428, 95% CI = 1.14–1.64, p < 0.01), while booster vaccination in the last 130 days was the only protective factor that reduced mortality (p = 0.04, 95% CI = 0.43–0.99, OR = 0.66) among vaccinated patients (Table 4). Booster dose vaccination in the last 130 days reduced mortality by 33.8% (95% CI = 1–57) in vaccinated patients.

Table 1. Demographic characteristics and outcomes of patients hospitalized for COVID-19

	Total (n=742)		Vaccinated (n=564)		Unvaccinated (n=178)		P
	N	%	N	%	N	%	
Gender (Male)	342	46.1	267	47.3	75	42.1	0.22
Age (Mean±SD)	76.6±7.6		76.8±7.5		76.2±7.9		0.32
Disease Severity Non-Severe Severe Critically	 221 284 237	 29.8 38.3 31.9	 173 226 166	 30.6 40.0 29.4	 48 59 71	 27.0 33.1 39.9	**0.03**
CCI (Mean±SD)	5.5±1.7		5.6±1.6		5.1±1.8		**<0.01**
Hypertension	491	66.1	385	68.3	106	59.5	**0.03**
Diabetes Mellitus	284	38.3	234	41.5	50	28.1	**<0.01**
CAD	173	23.3	151	26.7	22	12.4	**<0.01**
Asthma/COPD	94	12.7	75	13.3	19	10.7	0.36
CKD	87	11.7	70	12.4	17	9.5	0.30
CHF	77	10.4	61	10.8	16	9.0	0.69
Others	60	8.1	45	8.0	15	8.4	
Wbc (10^3/uL) (Mean±SD)	7.54±5.01		7.56±5.25		7.47±4.17		0.95
Ferritin (µg/L) (Mean±SD)	590±768		551±749		714±817		**<0.01**
CRP (mg/L) (Mean±SD)	103±79		106±79		96±80		0.09
Procalcitonin (ng/mL) (Mean±SD)	0.89±5.25		0.83±4.73		1.07±6.66		0.89
Creatinine (mg/dl) (Mean±SD)	1.35±1.23		1.40±1.34		1.19±0.77		0.06
ALT (IU/L) (Mean±SD)	26±25		24±24		30±27		**<0.01**
AST (IU/L) (Mean±SD)	37±39		35±39		42±41		**<0.01**
D-dimer (µg FEU/mL) Mean±SD)	1.12±1.65		1.09±1.65		1.20±1.63		0.12
Length of (Mean±SD) hospital stay (days)	13.9±10.8		13.6±10.6		14.9±11.5		0.13
ICU admission	217	29.2	151	26.8	66	37.1	**0.01**
Invasive mechanical ventilation	206	27.8	143	25.4	63	35.4	**0.01**
Mortality	194	26.1	136	24.1	58	32.6	**0.03**

CCI: Charlson Comorbidity Index, CAD: Coronary artery disease, COPD: *Chronic obstructive pulmonary disease, CKD: Chronic Kidney Disease, CHF:* Chronic heart failure, *ICU: Intensive care unit*

Table 2. Mortality rates of COVID-19 patients by comorbidity and vaccination status

		Total		Vaccinated		Unvaccinated		p	OR
	Death	N	%	N	%	N	%		
Hypertension	No	371	76.6	297	77.1	74	69.8	0.12	0.69
(n=491)	Yes	120	24.4	88	22.9	32	30.2		
DM	No	215	75.7	180	76.9	35	70.0	0.30	0.70
(n=284)	Yes	69	24.3	54	23.1	15	30.0		
CAD	No	124	71.7	108	71.5	16	72.7	0.91	1.06
(n=173)	Yes	49	28.3	43	28.5	6	27.3		
Asthma/COPD	No	70	84.3	57	87.5	13	82.6	0.50	0.68
(n=94)	Yes	24	15.7	18	12.5	6	17.4		
CKD	Yes	55	63.2	46	65.7	9	52.9	0.33	0.59
(n=87)	No	32	36.8	24	34.3	8	47.1		
CHF	No	54	70.1	44	71.0	10	66.7	0.75	0.82
(n=77)	Yes	23	29.9	18	29.0	5	33.3		

DM: Diabetes Mellitus, CAD: Coronary artery disease, COPD: *Chronic obstructive pulmonary disease, CKD: Chronic Kidney Disease, CHF:* Chronic heart failure,

Table 3. Comparison of characteristics of survived anddeceased in vaccinated patients

		Survivors (n=428)		Non-Survivors (n=136)		p	OR
	N	N	%	N	%		
Gender (Male)	267	197	46.0	70	51.5	0.27	1.25
Age (Mean±ss)	564	76±7		79±8		**0.01**	
Number of Vaccines 2 dose 3 dose	 283 281	 205 223	 47.9 52.1	 78 58	 57.4 42.6	0.05	0.68
Post-vaccine Duration ≤130 days >130 days	 250 314	 200 228	 46.7 53.3	 50 86	 36.7 63.3	**0.04**	0.66
CCI (Mean±ss)	564	5.4±1.5		6.2±1.8		**<0.01**	
Hypertension	385	297	69.4	88	64.7	0.31	0.81
Diabetes Mellitus	234	180	42.0	54	39.7	0.63	0.91
CAD	151	108	25.2	43	31.6	0.14	1.37
Asthma/COPD	75	57	13.3	18	13.2	0.98	0.99
CKD	70	46	10.7	24	17.6	**0.03**	1.78
CHF	62	44	10.3	18	13.2	0.34	1.33

CCI: Charlson Comorbidity Index, CAD: Coronary artery disease, COPD: *Chronic obstructive pulmonary disease, CKD: Chronic Kidney Disease, CHF:* Chronic heart failure,

Table 4. Multivariate analysis of factors that cause need ICU admission and death in vaccinated patients

	Multivariate Analysis for ICU Admission			Multivariate Analysis for Mortality		
	OR	95 %CI	P	OR	95 %CI	P
Age	1.02	0.99-1.05	0.13	1.03	0.99-1.05	0.07
Charlson Comorbidity Index	1.25	1.11-1.41	**<0.01**	1.28	1.14-1.46	**<0.01**
Post-vaccine Duration (≤130 days)	0.69	0.46-1.02	0.06	0.66	0.43-1.00	**0.04**

DISCUSSION

Older adults, who are most vulnerable to the devastating impact of the COVID-19 pandemic, comprise of a significant proportion of COVID-19-related deaths during the pre-vaccine period (8). In this study, we presented a detailed analysis of the demographic characteristics, clinical findings, and outcomes of 564 vaccinated and 178 unvaccinated patients aged ≥ 65 years hospitalized for COVID-19 in a pandemic epicenter. We found that 26% of older patients with COVID-19 died. Vaccination with at least a double dose of CoronaVac reduced the need for intensive care and mortality by approximately 25%. In addition, delaying booster vaccination for > 130 days increased mortality by 52%.

The main purpose of vaccination in older adults is to protect against serious COVID-19 and its fatal consequences. Immune senescence, general fragility, mental and psychosocial health problems, underlying diseases, and nutritional disorders are important problems that reduce vaccine efficacy in older populations (1). Compared to the Pfizer-BioNTech and Oxford-AstraZeneca vaccines, fewer population-based analyses have studied the efficacy of the CoronaVac vaccination in older adults (9-11) In studies evaluating the antibody levels induced by the CoronaVac, it was shown that post-vaccine seropositivity rates were similar to young adults, and neutralizing antibody titers were lower in elderly people (4,12). In addition, neutralizing antibody levels against SARS-CoV-2 variants in the CoronaVac vaccine have also been reduced (13,14).

In the population-based ESPERANZA cohort, which included people ≥ 60 years of age, approximately 2,830,000 individuals were evaluated over a seven-month period. In the ESPERANZA study, the effectiveness of CoronaVac was found to be lower than that of the Pfizer-BioNTech and Oxford-AstraZeneca. In addition, researchers showed that with increasing age, the effectiveness of CoronaVac decreased more than that of other vaccines. CoronaVac was found to reduce hospitalization without death by 47.3% and with death by 72.1% in people aged ≥ 60 years (9). Ranzani et al. reported that CoronaVac was 46.8% effective against symptomatic COVID-19, 55.5% effective against COVID-19-related hospitalization, and 61.2% effective against COVID-19-related deaths during the gamma variant predominant period. In addition, they found that the effectiveness of CoronaVac decreased to 30–40% in people aged > 80 years (10). In another population-based study, CoronaVac was reported to reduce mortality in older adults during the gamma variant dominant period (11). In our hospital, we did not routinely perform SARS-CoV-2 genotyping, but more than 90% of the SARS-CoV-2 variants determined in COVID-19 patients in our country were delta during the study period and the omicron variant had not yet been detected. In the present study, CoronaVac reduced mortality by 25%, and this rate was lower than the results of other studies (9-11).

However, since we evaluated patients who required hospital admission, we found that the effectiveness of CoronaVac on mortality was relatively low. In addition, the decreased effectiveness can probably be explained by the fact that the study was conducted in the more deadly delta variant-dominant period and the time elapsed after vaccination was prolonged. Therefore, we evaluated the impact of delayed booster doses and found that in-hospital mortality was lower in recently vaccinated patients.

Many studies have revealed that COVID-19 patients with underlying diseases have increased risk of poor prognosis (15-18). In the study of Yavuz et al., chronic pulmonary disease, malignancy, chronic kidney disease, and cardiovascular diseases were reported as independent risk factors for mortality (17). In the study by of Sezen et al., mortality was found to be significantly higher in patients with CCI ≥ 1 (18); however, there is a limited number of studies evaluating the effect of comorbid diseases on prognosis in patients with CoronaVac. In our study, increased CCI was an independent risk factor for mortality in patients aged ≥ 65 years regardless of vaccination status. Among vaccinated patients, those patients with chronic kidney disease had an approximately two-fold increased risk of death.

There is no consensus regarding when the booster dose of CoronaVac vaccine should be administered. However, studies evaluating neutralizing antibody titer levels have reported that the optimal timing for a booster dose is 6–8 months (19-20). WHO stated that a booster dose can be administered to high-risk groups 4–6 months after completion of the primary CoronaVac vaccination series (21). In our study, delaying the booster dose for > 130 days in patients aged ≥ 65 years was associated with a 1.5-fold increase in mortality. Therefore, we deduced that patients aged ≥ 65 years with primary vaccination with CoronaVac should receive booster doses earlier because of decreased cellular immune response against SARS-CoV-2 variants and increased mortality.

Many studies have compared heterologous vaccines (a different vaccine product from CoronaVac) and homologous vaccines as a booster vaccine (22-23). In a population-based study conducted by Jara et al., the homologous CoronaVac vaccine was less effective than heterologous vaccination (booster dose Pfizer-BioNtech or Oxford-AstraZeneca) in preventing symptomatic COVID-19, COVID-19-related hospitalization, need for ICU admission, and death (22). In the study conducted during the delta variant dominant period by Suah et al., homologous CoronaVac vaccination was less effective in preventing COVID-19 than heterologous (booster dose Pfizer-BioNTech or Oxford-AstraZeneca) vaccination (23). In our study, mortality was similar in patients who received a booster dose of CoronaVac and those with a booster dose of Pfizer-BioNTech.

This study had several strengths. First, only older patients (≥ 65 years old) were included in the study. Thus, we ensured patient homogenization by reducing age-related confounding conditions. Second, to our knowledge, this is the first study to determine the predictors of mortality in vaccinated older adults with COVID-19 in our country. Third, we adjusted the independent covariates including age and comorbidty index by the multivariate analysis. However, our study had some limitations. First, this cross-sectional study was conducted at a single center. Second, only hospitalized patients with confirmed COVID-19 were included in this study. Therefore, the effectiveness of vaccination with CoronaVac against COVID-19 development and against COVID-19-related hospitalization could not be evaluated.

CONCLUSION

In conclusion, CoronaVac vaccination improved survival in hospitalized older adult patients (≥ 65 years old) with COVID-19. However, delaying the booster dose for more than 130 days were significantly associated with decreased survival. Therefore, older adults who completed their primary vaccination se-

ries with CoronaVac should not delay their booster dose to reduce the risk of death.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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